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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/718,765	11/21/2003	Rima Kaddurah-Daouk	AVZ-001CPUSCN2	1461

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EXAMINER	
LUNDGREN, JEFFREY S	
ART UNIT	**PAPER NUMBER**
1639	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/10/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/718,765	KADDURAH-DAOUK ET AL	
	Examiner	Art Unit	
	Jeff Lundgren	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 August 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-23* is/are pending in the application.

4a) Of the above claim(s) *9-11,18 and 21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,12-17,19,20,22 and 23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

Claims 1-23 are pending in the instant application; claims 9-11, 18 and 21, are withdrawn; claims 1-8, 12-17, and 19, 20, 22 and 23 are the subject of the Office Action below.

This application contains claims 9-11, 18 and 2,1 drawn to an invention nonelected with traverse. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144). See MPEP § 821.01.

Information Disclosure Statement

The information disclosure statement filed December 18, 2006, fails to fully comply with 37 CFR 1.98(a)(2), which requires: (i) a legible copy of each cited foreign patent document; and (ii) a copy of an English-language translation of all non-English-language documents, or portion thereof. Accordingly, certain documents cited on the Form-1449 provided without a copy, or provided in a language other than English, have been lined through and have not been considered.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 19-23 are rejected under 35 U.S.C. § 101 for being wholly inoperative and lacking a credible utility.

Specifically, Applicants claim a method for "*eliminating Huntington's disease.*" However, Applicants fail to provide a credible assertion that such a method exists. Situations where an invention is found to be "inoperative" and therefore lacking in utility are rare, and rejections maintained solely on this ground by a Federal court even rarer. In many of these cases, the utility asserted by the applicant was thought to be "incredible in the light of the knowledge of the art, or factually misleading" when initially considered by the Office. In re Citron, 325 F.2d 248, 253, 139 USPQ 516, 520 (CCPA 1963). Other cases suggest that on initial

evaluation, the Office considered the asserted utility to be inconsistent with known scientific principles or "speculative at best" as to whether attributes of the invention necessary to impart the asserted utility were actually present in the invention. In re Sichert, 566 F.2d 1154, 196 USPQ 209 (CCPA 1977). However cast, the underlying finding by the court in these cases was that, based on the factual record of the case, it was clear that the invention could not and did not work as the inventor claimed it did. Indeed, the use of many labels to describe a single problem (e.g., a false assertion regarding utility) has led to some of the confusion that exists today with regard to a rejection based on the "utility" requirement. Examples of such cases include: an invention asserted to change the taste of food using a magnetic field (Fregeau v. Mossinghoff, 776 F.2d 1034, 227 USPQ 848 (Fed. Cir. 1985)), a perpetual motion machine (Newman v. Quigg, 877 F.2d 1575, 11 USPQ2d 1340 (Fed. Cir. 1989)), a flying machine operating on "flapping or flutter function" (In re Houghton, 433 F.2d 820, 167 USPQ 687 (CCPA 1970)), a "cold fusion" process for producing energy (In re Swartz, 232 F.3d 862, 5 USPQ2d 1703, (Fed. Cir. 2000)), a method for increasing the energy output of fossil fuels upon combustion through exposure to a magnetic field (In re Ruskin, 354 F.2d 395, 148 USPQ 221 (CCPA 1966)), uncharacterized compositions for curing a wide array of cancers (In re Citron, 325 F.2d 248, 139 USPQ 516 (CCPA 1963)), and a method of controlling the aging process (In re Eltgroth, 419 F.2d 918, 164 USPQ 221 (CCPA 1970)). These examples are fact specific and should not be applied as a per se rule. Thus, in view of the rare nature of such cases, Office personnel should not label an asserted utility "incredible," "speculative" or otherwise unless it is clear that a rejection based on "lack of utility" is proper.

The disclosed invention is inoperative and therefore lacks utility.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

The rejection of claims 1-8, 12, 13, 15-17, 19 and 20, are rejected under 35 U.S.C. § 103(a)[1] as being unpatentable over Ericinska *et al.*, *Journal of Cerebral Blood Flow and Metabolism 9*:2-19 (**1989**), in view of Beal *et al.*, *Journal of Neurochemistry 57(3)*:1068-1073 (**1991**), in view of Roberts *et al.*, *American Journal of Physiology 243(6)*:H911-H916 (**1982**)[2], is maintained.

Applicants generally allege that the references, either alone or in combination, do not teach the claimed invention. Applicants argue each of the references individually, and have not considered the art as a whole.

The claims are directed to methods of treating certain CNS disorders/diseases, such as Huntington's disease *via* the administration of creatine analogs.

Ericinska teaches an in depth overview of the CNS metabolic system, including the role of creatine, creatine phosphate and creatine kinase, and that a major pathological component of CNS complications is ATP depletion. Ericinska states:

> Brain, like all other organs in the body, contains phosphorylated nucleotides that yield energy upon hydrolysis of their phosphate bond(s); the most important of these is the adenine nucleotide ATP. In addition, the CNS, in common with other excitable tissues possesses another high energy reservoir, the creatine phosphate/creatine (PCr/CR) system, which

[1] This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

[2] The teachings of Walker (Walker, Guanidino Compounds in Biology and Medicine, pages 187-194 (1992)) are comprehensive of the teaching of Roberts, and accordingly is made as an alternate/addition rejection under 35 U.S.C. § 103(a).

> is linked to the adenine nucleotides through a rapid equilibration in the creatine phosphokinase reaction..."

Ericinska, at page 2, col 2, last paragraph.

Beal presents a model relating Huntington's disease to the depletion of ATP levels. Beal shows that when AOAA is introduced to striatal tissue that ATP levels were depleted, and resulted in striatal lesions that closely resemble Huntington's disease both neurochemically and histologically. Beal teaches:

> "Intrastriatal injections of AOAA resulted in fourfold significant increases of striatal lactate levels and significant decreases in ATP concentrations. AOAA may therefore induce an intracellular equivalent tissue ischemia. It is of interest that AOAA lesions are similar to ischemic brain damage in that they are attenuated by pentobarbital, presumably owing to its ability to lower cerebral metabolic rate, and they show sparing of NADPH-diaphorase neurons."

Beal, at page 1071, col. 2, last paragraph, through page 1072, col. 1 (citations omitted).

However, neither Ericinska nor Beal explicitly teach the administration of creatine analogs as a means of maintaining higher levels of CNS/brain ATP levels in treating CNS disorders associated with depleted ATP levels, such as Huntington's disease.

Roberts teaches the feeding of creatine analogs delays ATP depletion and the onset of rigor in ischemic heart tissue, and states that:

> "At the relatively high phosphorylation potentials that normally occur in aerobic cells, the creatine-P system effectively serves as a buffer-reservior for high-energy phosphate, and the [creatine-P]/[creatine] ratio provides a reliable measure of the cytosolic [ATP]/[free ADP] ratio at a given pH (20, 21)"

Roberts, at page H915, col. 2, first full paragraph.

One of ordinary skill in the art would have had a reasonable expectation of success in arriving at the claimed invention based on the combined teachings of Ericinska, Beal and Roberts (or Walker), because the art demonstrates the relationships that ATP levels and creatine levels have on the health of CNS tissues, and their relevance in Huntington's disease. Ericinska provides a detailed disclosure that explains the effects of ATP depletion and the role that creatine phosphate plays in the overall cellular physiology of CNS tissues, while Beal demonstrates the

pathophysiology of depleted ATP levels in CNS tissues, and the relationship it bears to Huntington's disease. Based on this understanding and the disclosed experimental results of Ericinska and Beal, one of ordinary skill in the art would have been motivated to treat disorders correlated with ATP-depletion via the administration of creatine and or creatine-phosphate because of the successful treatment illustrated by Roberts (or Walker). Accordingly, the invention as a whole is *prima facie* obvious.

The rejection of claim 14 under 35 U.S.C. 103(a) as being unpatentable over Ericinska, Beal and Roberts (or Walker) as applied to claims 1-8, 12, 13 and 15-17 above, and further in view of Nuti *et al.*, *Riv Neurol. 61(6)*:225-7 (**1991**), is maintained for the reasons set forth above.

Claim 14 is directed to a treatment of Huntington's disease using creatine and a steroid.

As discussed in the above rejection, the treatment using creatine/creatine-phosphate is obvious over Ericinska, Beal and Roberts; however, none teach the additional therapeutic of a steroid.

Nuti teaches that steroids are useful in the treatment of Huntington's disease:

> "Neuroleptic drugs represent the current therapy for Huntington's chorea (HC). However neuroleptics can improve involuntary movements, but not functional performance and disease progression. Several clinical and experimental data suggest the existence of functional relationship between corticosteroids and extrapyramidal system. We administered dexamethasone to six choreics, all female. Dexamethasone was given i.m. at dose of 4 mg/die for 20 days and 8 mg/die for 20 days more. Dexamethasone at both the doses used, determined significant improvement (p less than 0.05) of dyskinesia, evaluated by AIMS, and manual dexterity, evaluated by Tapping test. Although at present it is not clear which mechanism are responsible for this of dexamethasone favourable effect, it might open new perspectives in HC therapy."

Nuti, see abstract and detailed results.

One of ordinary skill in the art would have been motivated to additionally administer a steroidal compound as taught by Nuti, with the therapies of using creatine as taught by Ericinska, Beal and Roberts. One of ordinary skill in the art would have had a reasonable expectation of success in arriving at the claimed invention, because of the success of each treatment and the understanding that there are multiple mechanisms associated with Huntington's disease that may

be utilized for therapeutic treatments. Therefore, the invention as a whole was *prima facie* obvious at the time it was invented.

Conclusions

No claim is allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

If Applicants should amendment the claims, a complete and responsive reply will clearly identify where support can be found in the disclosure for each amendment. Applicants should point to the page and line numbers of the application corresponding to each amendment, and provide any statements that might help to identify support for the claimed invention (*e.g.*, if the amendment is not supported *in ipsis verbis*, clarification on the record may be helpful). Should Applicants present new claims, Applicants should clearly identify where support can be found in the disclosure.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Jeff Lundgren whose telephone number is 571-272-5541. The Examiner can normally be reached from 7:00 AM to 5:30 PM.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, James Schultz, can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

JSL

JAMES SCHULTZ, PHD.
PRIMARY EXAMINER